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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/659,578
Filing Date: September 10, 2003
Appellant(s): NAGY, ZSUZSANNA

June Cohan
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/08/2008 appealing from the Office action mailed 10/18/2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

The amendment after final rejection filed on 11/17/2008 has been entered.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Araga, S. et al., "Lymphocyte Proliferation and Subpopulations in Dementia of the Alzheimer Type", Jpn J Med, Vol. 29: pp. 572-575

Fischman, H. et al., "Sister Chromatid Exchanges and Cell Cycle Kinetics in Alzheimer's Disease", Biol Psych., Vol. 19 (1984): pp. 319-327

Nagy Z. et al., "The Cell Division Cycle And The Pathophysiology Of Alzheimer's Disease", Neurosci., Vol. 87 (1998), pp. 731-739

Nagy, Z. et al., "Cell cycle kinesis in lymphocytes in the diagnosis of Alzheimer's disease", Neuroscience Lett. Vol. 317 (2002): pp. 81-84

Nagy Z., "The dysregulation of the cell cycle and the diagnosis of Alzheimer's disease", Biochim Biophys Acta, Vol 1772 (2006 EPub): pp. 402-408

Chan, S. "Targeting the mammalian target of rapamycin (mTOR): a new approach to treating cancer", B J Cancer, Vol. 91 (2004): pp. 1420-1424

Wendel, H. "Survival signalling by Akt and eIF4E in oncogenesis and cancer therapy", Nature, Vol. 428 (2004): pp. 332-337

Callegari, A. et al., "UV irradiation induces a postreplication DNA damage checkpoint", PNAS, Vol. 103 (2006): pp. 15877-15882

Ichimura, K. et al., "Deregulation of the p14ARF/MDM2/p53 Pathway Is a Prerequisite for Human Astrocytic Gliomas with G1-S Transition Control Gene Abnormalities", Cancer Res, Vol 60 (2000)" pp. 417-424

Houtgraaf, J. et al., "A concise review of DNA damage checkpoints and repair in mammalian cells", Cardio Revascula Med, Vol 7 (2006): pp. 165-172

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 6, 8, 17, 30-32, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons set forth in the Office Actions dated 7/21/2005, 3/6/2007, 10/18/2007, and for reasons set forth below.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics,* Inc. 8 USPQD2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is a conclusion reached by weighing several factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQQ2d 1400 (Fed. Cir. 1988) and include the following:

Unpredictability of the art and State of the art. The art concerning diagnosis of Alzheimer's disease (AD) or associated neurological conditions only by assaying for a cell cycle defect at the G1/S transition is unpredictable. The claims are broad in nature and read on diagnosing AD by merely assaying for a G1/S checkpoint defect in any non-neuronal cell, in any

human subject, which could be a reduction in effectiveness of the checkpoint (i.e. as in claim 3), or an increase in the effectiveness of the checkpoint (within the scope of claim 1). Such assays that fall within the scope of the recited method steps (i.e. steps (A) and (B) as found in claim 1), but do not teach diagnosing any of the neurological conditions recited in claim 1, are well known in the art. The instant claims (e.g. claim 3) essentially read on assaying non-neuronal cells for resistance to a G1/S inhibitor such as rapamycin (used in the instant working example 1 as a G1/S inhibitor): i.e. rapamycin resistance would lead to a decrease in the length of the G1 phase relative to cells that are not resistant to rapamycin. See the lymphomas (lymphocytes as recited in instant claim 17) assayed and compared for rapamycin resistance or sensitivity by Wendel et al (page 333, second column, second full ¶ to page 334, second column) and the breast cancer cells taught by Chan et al (the abstract and page 1421, second column, second full ¶ in particular). Thus, the skilled artisan upon performing the claimed methods would associate such rapamycin resistance with certain cancer cells, there being no certain way to differentiate such a result between a diagnosis of cancer or one of the recited neurological conditions.

In a paper published five years after applicant's priority date, Nagy (2006) teaches that diagnosis of "definite" Alzheimer's can only be made by histopathological assessment after autopsy, and that clinical diagnostic criteria (NINCDS-ARDRA) have a very high false negative rate (see page 1, ¶ linking first and second columns). The instant specification teaches much the same (page 1, line 16 -page 2). Nagy et al (Neuro. Lett., 2002), using methods that appear to be the same as described in the instant specification, teach differences in the relative lengthening of the G1 phase upon rapamycin treatment of lymphocytes from control patients and from those already diagnosed using the NINCDS criteria (see page 82, second column, last ¶ to page 83,

second column, and Fig. 1). The lymphocytes from all patients diagnosed with some form of dementia (i.e. the preAD (pre-clinical AD), AD (probable AD), ADM (AD and other types of dementia), possAD (possible AD), and DNOS (dementia other than AD) groups) were found to be less responsive to rapamycin than the control cells in the G1 lengthening assay (Fig. 1A). This is significant because: 1) these results are different than those presented in the instant application (e.g. compare Fig. 1A of Nagy et al (2002) with Fig. 2 of the instant application, in particular the possAD and DNOS groups relative to the control, and the AD and ADM groups relative to each other); and, 2) without prior diagnosis of the patients using the NINCDS criteria, as taught by Nagy et al, there could be no diagnosis of AD, such prior diagnosis not being a limitation of the instantly claimed methods. Regarding 1) above, this discrepancy calls into question the reliability and predictability of the instantly claimed methods. Regarding 2) above, in Fig. 1A of Nagy et al (2002), the DNOS group is less responsive to rapamycin than the control. According to the instantly claimed methods, this would lead to a misdiagnosis of these patients as having AD, which is clearly not correct. The same would be true if the G1/S diagnostic assay for AD was performed as described in Figs. 3 and 5 of the instant specification, in which the DNOS group represented the most resistance to rapamycin or H_2O_2 treatment in the age-corrected graphs. These same experiments, as reported by Nagy et al (2002, Figs. 1B and 1D), appear to use data without age-correction, which is questionable in the diagnosis of AD (see the Office Action dated 7/21/2005, page 5). Nevertheless, the rapamycin effect on patient cells was concluded to have no significant difference from controls, and the H_2O_2 effect did not differentiate between the controls and the preAD patients.

The instantly claimed methods and specification ignore the fact that merely assaying for a defect in the G1/S checkpoint, or relative resistance to the effects of a G1 inhibitor such as rapamycin, then diagnosing patients with such a G1/S defect as having AD would misdiagnose many cancer patients as having AD. See the explanation above. Furthermore, a G1/S defect could exist within a patient without any outside symptoms of cancer because it has become appreciated that cancer is a development of a series of defects in cell growth regulation, e.g. a series of oncogenic mutations which arise over time or are inherited. Thus, a patient may have a resistance to rapamycin due to a G1/S defect, but not necessarily exhibit cancer symptoms because other mutations have not arisen. See, e.g., Ichimura et al (2000), who teach a G1/S defect is often found in gliomas, but also often requires, *inter alia*, a p53 mutation. Absent evidence to the contrary, testing the rapamycin-resistant cells above or otherwise normal cells having a G1/S defect using the instantly claimed methods would produce results similar to those seen for the AD cells, i.e. a resistance to the effects of rapamycin. The claims require no further diagnostic steps and thus would lead the skilled artisan to mis-diagnose such cells as being AD or AD-associated when they are actually suffering from am entirely different disease.

Given the above, the state of the art regarding the diagnosis of AD or related neurological conditions only by assaying for a G1/S checkpoint defect is poorly developed. The development of such an assay would have to be done empirically.

Number of working examples. Applicants have provided no working examples of diagnosing AD or related neurological conditions by merely performing a G1/S checkpoint assay as instantly claimed. The disclosed working examples require a prior diagnosis of patients using

the NINCDS criteria, and a comparison of the groups diagnosed by such criteria in a G1 phase lengthening assay.

Amount of guidance. Applicants provide no direction or guidance for diagnosing AD, or any other neurological condition, by performing only the method steps as instantly claimed (e.g. see claim 1). The specification requires the skilled artisan to practice trial and error experimentation to develop a reliable and effective assay that differentiates AD from other dementias and cancer by merely assaying for a G1/S checkpoint defect.

Scope of the invention. The claims are broad in nature and read on diagnosing AD and related neurological conditions by merely assaying for a G1/S checkpoint defect in any non-neuronal cell, which could be a reduction in effectiveness of the checkpoint (i.e. as in claim 2), or an increase in the effectiveness of the checkpoint (within the scope of claim 1). There is no description or guidance for such an assay for an increase in the effectiveness of the G1/S checkpoint, let alone an association of such an increase with AD or a neurological condition. The claims in general are not limited to any specific G1 inhibitor, and certain cell cycle arrest stimuli recited in claim 6 do not specifically arrest cells in G1, but rather G2 or other phases of the cell cycle (i.e. ionizing and UV radiation, see Callegari and Houtgraaf et al). Lengthening of the S and G2/M phases of the cell cycle by this arrest would give spurious results in the assay set forth in the specification to measure G1 lengthening, i.e. BrdU incorporation followed by FACS analysis. The instant application does not teach how to practice the claimed methods, i.e. assaying for a specific block in the G1/S transition, using stimuli that induce arrest throughout the cell cycle, i.e. stimuli that are not specific to G1/S.

Nature of the invention. The invention involves the unpredictable art of diagnosing AD.

Level of skill in the art. While the level of skill in the art of assaying for cell cycle defects is high, the level of skill in the art of diagnosing AD by assaying for such defects is low. The unpredictability of the art, lack of guidance, broad scope of the claims and poorly developed state of the art would require that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Claims 1-3, 5, 6, 8, 17, 30-32, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons set forth in the Office Action dated 10/18/2007, and for reasons set forth below.**

Claim 1 (from which all other claims depend, amended in the response dated 8/6/2007) recites, in part (B), a step of comparing a determined G1/S cell cycle checkpoint effectiveness with "the G1/S cell cycle checkpoint effectiveness exhibited by…an individual having said neurological condition". As best understood, the claim then requires the skilled artisan from this

comparative information to diagnose which one of the several neurological conditions recited in claim 1 the subject might have. The response of 8/6/2007 indicates support for the amendment may be found on pages 3-6, 9, 10 and 23-30. These passages do not recite a step of comparing the determined G1/S effectiveness with that of "an individual having said neurological condition." Rather, a review of the specification and claims as originally filed discloses that the determined G1/S effectiveness of the subject is to be compared to control cells from either healthy patients, or to cells that do not have a cell cycle regulatory defect. Thereafter, they are then classified into one of the neurological conditions recited in claim 1 using NINCDS criteria, i.e. as taught in Example 1. There is no mention or teachings of a method step of diagnosing a subject as having one of the neurological conditions recited in claim 1 by merely comparing a G1/S cell cycle checkpoint effectiveness of subject cells to those of "an individual having said neurological condition" Therefore, there appears to be no support for the method step of diagnosing one of the neurological conditions in claim 1 by comparing a determined G1/S cell cycle checkpoint effectiveness with "the G1/S cell cycle checkpoint effectiveness exhibited by…an individual having said neurological condition". Thus, the amended claims include impermissible New Matter.

(10) Response to Argument

Applicant's arguments filed 11/18/2008 have been fully considered but they are not persuasive.

The 35 USC 112 1st ¶ enablement rejection

Applicants essentially assert that: 1) the Examiner has virtually ignored the declaration by inventor Zsuzsanna Nagy (the Nagy Declaration), which states that: the instant claims recite a method to reliably diagnose AD; there is no contradictory data to be found between the instant specification and the art of record; and there is sufficient guidance provided by the instant application to enable the claimed invention; 2) the burden of making a *prima facie* case for rejection is upon the Examiner, and should be based upon the Wands Factors; 3) performing routine assays such as FACS, is not undue experimentation; 4) the present specification provides sufficient guidance and working examples to enable the claimed invention without use of the NINCDS criteria, which were merely used to confirm a diagnosis; 5) the Nagy Declaration addresses the misdiagnosis of cancer patients by the instant methods, primarily because non-cancerous cells would not be tested, and the testing of cancerous cells would not present a problem in the claimed methods because additional steps are not excluded by the claim language "comprising", such further steps would be used because one skilled in the art would not rely upon a single test to be conclusive, and would use prior training and judgment, along with a patients medical profile; 6) the present invention relates to diagnostic molecular biology, which is a well-advanced field, along with considerable knowledge in the art studying the cell cycle; 7) the Nagy Declaration states that the claimed methods are at least as useful, reliable, and specific as current methods, e.g. the NINCDS criteria, and that the data from the instant application do not contradict that found in Nagy et al (2002); 8) the Examiner dismisses the points in the Nagy Declaration with mere dismissal; 9) enablement is satisfied when undue experimentation is not required, and the present specification guides one of skill in the art to check the G1/S checkpoint

to diagnose AD; 10) the breadth of the instant claims should not be interpreted to include increased and decreased effectiveness of the cell cycle checkpoint.

Regarding 1), all of the points in the Nagy Declaration were addressed in the Final Action dated 10/18/2007. Applicants point to no specific points of the Nagy Declaration that were "ignored." Rather than being ignored, the Nagy Declaration was found to be unconvincing for reasons made of record.

Regarding 2), a review of the prosecution of record reveals an extensive analysis of the Wands Factors (reiterated above) and the relevant art.

Regarding 3) and 6), it was not alleged that the skilled artisan could not perform routine assays, such as FACS or diagnostic molecular biology, nor that they were laborious. The relevant point is that the specification requires the skilled artisan to practice laborious trial and error experimentation to develop a reliable and effective assay that differentiates AD from other dementias and cancer by merely assaying for a G1/S checkpoint defect, i.e. the claimed invention. Again, the Examiner has never alleged that routine assays associated with the claimed invention are not enabled. Indeed, as set forth above, testing for rapamycin resistance was well-known, but, was associated with cancerous cells, not Ad or related conditions.

Regarding 4), the disclosed working examples, and pages 23-30 as indicated by applicants, use the NINCDS-ARDRA (NINCDS) criteria to compare the G1/S experimental data. The indicated passages of the specification only indicate the G1/S experiments were done blind, whereas the comparison (i.e. step (B) of claim 1) was done in conjunction with the already determined NINCDS criteria. Thus, the working examples relied upon the NINCDS criteria to classify the patient/subject samples into the neurological conditions found in Fig. 2, for example,

and as recited in claim 1. There is no disclosure of diagnosing subjects having one of the specific neurological conditions recited in claim 1 without use of the NINCDS criteria.

Regarding 5), it is noted that the features upon which applicant relies (i.e., testing non-cancerous cells, performing other diagnostic steps, testing cells from elderly individuals only, use of "judgment" and patient profile, using abnormal blood tests suggestive of cancer, not testing cancerous cells or a tumor biopsy, testing based on longevity of the patient) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims remain extremely broad, and read on testing any non-neuronal cells, including lymphocytes, which are specifically recited (claim 17), from any human subject, regardless of age, health, etc. Thus, the claims encompass testing cells from patients that may or may not have cancer, and specifically lymphocytes from such a patient. Absent evidence to the contrary, and as only a limited example of non-neuronal cells, leukemia or lymphatic cancer cells would be found in this group of cells. The fact remains that cancerous cells with a G1/S defect, as exemplified by the rapamycin resistant cells taught in the art of record, would give a false positive result in the claimed methods (see the analysis above). Arguments that one of skill in the art would know *a priori* what cells and what patients to test are unconvincing given the claimed scope, as are the performance of method steps that are not recited in the claims. Furthermore, the Examiner is unaware of how the skilled practitioner could determine cancerous cells from non-cancerous cells without some kind of test, be it an X-ray, blood test, etc., as the Nagy Declaration asserts on page 7. Cancerous cells exist outside of tumors, e.g. tumors metastasize, and cancer exists in non-tumorous forms, e.g. leukemia.

Finally, a G1/S defect could exist within a patient without any outside symptoms of cancer, see the analysis set forth above, as exemplified by Ichimura et al (2000), who teach a G1/S defect is often found in gliomas, but also often requires, *inter alia*, a p53 mutation.

Regarding 7), the Nagy declaration compares different data than that alleged by the Examiner to be "unreliable." The Nagy declaration compares two sets of so-called "relative" G1 lengthening data, i.e. Fig. 1A from the Nagy et al and the left-hand chart from Fig. 2 of the application, both of which appear to have not been age-corrected (there is no mention of age-correction in Nagy et al 2002). The Examiner agrees that these graphs are similar, but this misses the point set forth in the previous Office Actions on two important grounds: 1) ample evidence that only age-corrected data should be used in Alzheimer's disease (AD) diagnosis has been presented in the previous Office Actions (e.g. see page 5 of the 7/21/2005 Office Action), this is because without such correction, any differences seen in experimental data may be due to age differences between the controls and subjects, not a difference due to the subject having AD; 2) the claims are not limited to any manipulation of the data regarding age-correction, hence, they encompass both situations set forth in Fig. 2 of the instant specification. If one compares these graphs (or to Fig. 1A in Nagy et al 2002), as set forth in the previous Office Action, one draws several different conclusions, in firm support of the Examiners conclusions of unreliability and the inability of the instant method to diagnose AD commensurate in scope with the claims. To review, a strict reading of the claims in light of the data set forth in Fig 1A of Nagy et al (2002) and the left hand graph of the instant Fig. 2 leads to the incorrect diagnosis of the DNOS group as having AD, and possibly would not lead to the diagnosis of members of the possAD group as having AD (i.e. see the error bars of the possAD group in Fig. 2, left hand graph).

Already the method has created false positives in three DNOS subjects (Table 1a of the specification) and an unknown number of false negatives in the possAD group, and this does not even take into account errors introduced by not applying age correction, the large number of false negatives known to be missed by current methods of AD diagnosis, and the number of false positives introduced by the testing of cancerous cells with a G1/S defect.

On the other hand, a strict reading of the claims in light of the data set forth in Fig 1A of Nagy et al (2002) and the right hand graph of the instant Fig. 2 leads to different diagnosis of the possAD, ADM, and DNOS groups. This is the basis for the unreliability set forth in the previous Office Action, i.e. depending on how the data are manipulated, opposing results are generated for the same subjects. According to the teachings of the prior art, the right hand graph of Fig. 2 (age-corrected) should be used. Doing so would improve the misdiagnoses of the DNOS group as having AD when the left hand graph is used, but aggravates the situation with the false negative diagnosis of the possAD group and introduces questionability as to which individuals in the ADM group should be diagnosed with AD, if any. Table 1a of the specification indicates the possAD group had 3 subjects and the ADM group 7 subjects, out of a total of 35 subjects and 14 controls. If the 10 members of the ADM and possAD groups were misdiagnosed, the assay is only 71% accurate. This number does not take into account the problems set forth above, i.e. the known false negative rate inherent to AD diagnoses methods, and the false positives generated by testing cancerous cells. Furthermore, in this respect, the instant methods are less sensitive and reliable than the NINCDS criteria, which did diagnose the possAD and ADM groups.

Regarding 8), the Examiner has presented an extensive analysis of this data in the Final Action dated 10/18/2007, and reiterated above. It is unclear how this can be construed as

"dismissal." Rather, the analysis of the data was an unconvincing argument for patentability, as it points out the unreliability of the claimed diagnostic methods, and their poor performance relative to known methods (i.e. NINCDS criteria).

Regarding 9), the claims are broad in nature and read on diagnosing AD or related neurological conditions by merely assaying for a G1/S checkpoint defect in any non-neuronal cell, in any human subject, which could be a reduction in effectiveness of the checkpoint (i.e. as in claim 3), or an increase in the effectiveness of the checkpoint (within the scope of claim 1). Doing so requires undue experimentation for the extensive reasons set forth above.

Regarding 10), a reading of the specification and the data set forth in Fig. 2 teaches that variance in the length of the G1/S checkpoint can either be less than or greater than (i.e. an increase in the effectiveness of the checkpoint) a given control or starting point. See Fig. 2, left hand graph, as one example wherein the possAD group variance sets forth that the length of the G1/S checkpoint was greater, i.e. more effective, relative to controls. Furthermore, the specification provides no link between an increase in G1 effectiveness and diagnosis of AD.

The 35 USC 112 1st ¶ written description rejection

Applicants essentially assert that: 1) the Examiner argues that there is no written description because the exact claim language is not found within the specification; 2) the specification discloses comparison of the G1/S checkpoint data for subject cells with such data from control cells, which may be from subjects having the neurological conditions recited in claim 1.

Regarding 1) and 2), it was never alleged by the Examiner that the claims lack written description because the exact claim language is not found in the specification. Rather, the analysis relied upon the teachings of the entire specification. There simply is no support for a method wherein the specific neurological conditions recited in claim 1 are diagnosed by merely comparing the effectiveness of a G1/S checkpoint with individuals having said neurological condition(s). The specification, in particular the exact passages pointed out by applicants as providing support for the claimed invention, requires use of the NINCDS criteria to provide classification into the specific conditions recited in claim 1. As the use of such criteria is not recited in the claims, the methods encompassed by claim 1 are significantly broader than those disclosed by the invention as originally filed.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Michael Burkhart/

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